

REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1, 3, 6, 8, 11-13, 15, 18-21, 24-26, and 73 are pending with entry of this amendment. Claims 3, 8, 15, and 22-23 are cancelled herein and claims 1, 6, 13, 18, 19, 21, 24, and 73 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. For example, the amendments to the independent claims add a limitation from previously existing dependent claims describing the types of agonists that might be used for immune suppression. One type of agonist added, an antibody fragment, was not included in the previous dependent claim, but support can be found in the specification, e.g., on page 22, in the last paragraph which defines an antibody to include antibody fragments. Claim 24 is amended herein to clarify that the agonist modulates the immune system independent of the polarity of the immune response, which is supported in the specification as filed, e.g., on the last paragraph of page 71. Claims 21 and 73 are amended herein to delete diseases to which the Examiner objected and therefore add no new matter to the application. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Priority Claims are Proper

Benefit of the filing dates of provisional application 60/444,494, filed January 31, 2003, and provisional application 60/519,074, filed November 10, 2003, was not acknowledged by the Examiner. As described in detail below, Applicants have presented a proper priority claim to both documents and respectfully request that the relevant priority claims be properly acknowledged.

The Office asserts that benefit of provisional application 60/444,494, filed on January 31, 2003 cannot be granted because it is a collection of papers and the inventors are not listed as authors on some of them. While it may be true that the provisional applications are copies of articles for publication, the articles fulfill the requirements of 35 U.S.C. § 112 and therefore the present application properly claims benefit of the provisional application. As for the fact that the inventors are not authors on some of the publications, Applicants

respectfully point out that the papers on which the inventors are not listed as authors are included in the provisional application as background material to highlight the novelty of the claimed invention, i.e., the fact that the role of the IL-27R receptor presented in the prior art and the one presented by the claimed invention are totally different, in fact opposite. These publications show that one of skill in the art at the time the application was filed would not have used an agonist of IL-27R to suppress the immune system; one of skill in the art looking to suppress the immune system through the IL-27R receptor would have used an antagonist. For example, one publication presents the sequence of the receptor and the gene encoding it and the other two publications clearly point out that the Th1 immune response was thought to be impaired in the absence of IL-27R; therefore, based on the prior art, one would have used an antagonist of IL-27R to suppress a Th1 immune response – not an agonist as claimed. Furthermore, the style or format the provisional application takes is immaterial as long as it adequately describes and enables the invention, as the provisional application at issue does. Applicants therefore respectfully request that benefit of the provisional application be acknowledged.

In addition, the Office alleged that neither provisional application corresponds to the scope of the claims in the instant application. The rejection focused on gene therapy and alleged that agonists are not taught in the provisional applications. Applicants respectfully traverse in part and amend in part. As the scope of the claim is changed herein, Applicants respectfully request that the Examiner reconsider the priority claims. However, Applicants also respectfully assert that the scope of the claims is fully supported by both provisional applications.

For example, in provisional 60/444,494 the inventive concept that the receptor for IL-27 is involved in control of the duration and intensity of immune responses in mammals is provided, e.g., in the 2nd column on page 10, where the role of IL-27R is described and proposed as a novel target for immune suppression. See, also, page 5, and pages 9-10 further describing the discovery that the absence of IL-27R leads to immune hyperactivity. One of skill in the art would know based on this data to activate, e.g., with an agonist, IL-27R to suppress the immune system. In fact, the abstract clearly states and the data fully support that the receptor is an "antagonist of T-cell mediated immune

hyperactivity." Therefore, one of skill would know, if the receptor antagonizes or blocks immune hyperactivity, to use an agonist or activator of the receptor to suppress the immune system as claimed. These concepts and data are reiterated in the 60/519,074 provisional application, e.g., at page 3, column 2, and page 10, column 2.

With regard to both provisional applications, the inventive concept is that of using an agonist of IL-27R to suppress the immune system. This is explained in both provisional applications. Even if no particular agonists, e.g., antibodies are presented in the applications, any person having ordinary skill in the art would know how to make an agonist antibody to a known receptor. It was well known in the art at the time the application was filed, that an agonist, e.g., an agonist antibody, could be used to activate a receptor and methods of making and identifying such agonists are also well known. The key concept embodied in the claimed invention is that activation of IL-27R can be used to suppress the immune system. This concept is fully supported in the specifications of both provisional applications and described in sufficient detail to enable the full scope of the claims. Applicants therefore respectfully request that the benefit claim be acknowledged.

Objections to the Specification

Applicants note with appreciation the Examiner's withdrawal of the objections to the specification.

Objections to the Claims

Applicants note with appreciation the Examiner's withdrawal of the objections to the claims.

35 U.S.C. §112, First Paragraph – The claims are enabled for their scope.

The claims were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office alleged that the claims are not enabled because they allegedly do not enable one of skill in the art to make and use the invention commensurate in scope with the claims. To expedite prosecution, Applicants

herein amend the independent claims to include the limitation that the agonist be IL-27, an active fragment of IL-27, or an agonistic antibody or antibody fragment.

In addition, Applicants herein amend the claims to include only those disorders that can be considered immune disorders and for which immune suppression would be an appropriate treatment. Applicants note however, that a patient may be suffering from any of a wide range of disorders, even one not typically considered an immune disorder and still be in need of immune suppression. However, the claims are amended herein, as suggested by the Examiner, to clarify which disorders are those in which immune suppression is especially desired. Some disorders are maintained in the claims even though they are considered non-immune disorders by the Office. For example, the Examiner requested that coronary artery bypass graft associated condition, Pityriasis rubra pilaris, prostatitis, a prostatitis related condition, congestive heart failure, myocardial dysfunction, and diabetes mellitus insulin resistance be removed from the Markush group as allegedly being non-immune conditions. Applicants respectfully disagree. For example, Pityriasis rubra pilaris is related to an abnormal immune response (see, e.g., www.emedicine.com/derm/topic337.htm). Prostatitis, which is inflammation of the prostate, would be appropriately treated with immune suppression as well as any graft associated condition and cachexia, which is an immune mediated wasting disease that affects muscle mass. For support that myocardial dysfunction and congestive heart failure can be properly included with immune disorders, see, e.g., "Pathophysiological Role of Cytokines in Congestive Heart Failure," Arnon Blum, Hylton Miller, *Annual Review of Medicine*, February 2001, Vol. 52, Pages 15-27. As provided in *Diabetes* 52:812-817, 2003, Spranger et al., "Inflammatory Cytokines and the Risk to Develop Type 2 Diabetes" a subclinical inflammatory reaction has been shown to precede the onset of type 2 (non-insulin-dependent) diabetes. Therefore, diabetes mellitus is also properly included as an immune disorder for which immune suppression is an appropriate treatment.

As the scope of the claims has changed, Applicants believe that the enablement rejection is moot. Applicants believe that the claims are enabled and respectfully request that the rejection be withdrawn.

35 U.S.C. §112, First Paragraph – The written description is adequate.

The claims were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleged that the subject matter of the claims is not described in such a way to convey to one of skill in the art that the inventors were in possession of the invention at the time the application was filed.

“The requirement for an adequate written description ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent.” M.P.E.P § 2162. To do so, a patentee must disclose sufficient information to put the public in possession of the invention. This requirement is met when the specification describes “the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.” M.P.E.P § 2163.

The written description provides support for the claims and shows that Applicant had possession of the invention at the time the application was filed. For example, a multitude of data is provided in the example section to show that IL-27R is not needed to generate a Th1 response to infection, but rather is needed to regulate the intensity and duration of the T cell response. Applicants then go on to show, e.g., in Example 4, that hyperactivity of the immune system is caused by the lack of IL-27R. See, also, the remaining examples providing further support for the idea that activation of IL-27R can be used to suppress an immune response. Therefore, the method is adequately described in the specification so that one of skill would know that Applicant was in possession of the invention, e.g., a method of suppressing the immune system through activation of IL-27R, e.g., with an agonistic ligand.

In particular, it was alleged in the Action that Applicants claim a genus while only describing a single species within that genus. Considering the amendments presented herein, the written description rejection is moot and Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §102.

The claims were rejected under 35 U.S.C. §§102(a) and 102(e) as allegedly anticipated by Timans et al.; under 35 U.S.C. §102(b) as allegedly anticipated by De Sauvage et al and by Bennet et al.; and under 35 U.S.C. §102(e) as allegedly anticipated by Matthews et al. Applicants respectfully traverse each rejection as discussed in detail below.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983).

The claims are not anticipated by Timans

The Office rejected the claims as allegedly anticipated by Timans under 35 U.S.C. §§102(a) and 102(e). On page 10 of the Action, it is alleged that Timans teaches administration of IL-27R agonists and antagonists "for therapeutic use in inflammatory conditions." Although Timans suggests the use of antagonists and agonists in inflammatory conditions, it does not specify that agonists be used for suppression of an inflammatory condition, as presently claimed. Therefore, it does not teach every element of the claims and cannot anticipate the claimed invention.

In particular, the Office relied on paragraph 39 in Timans for anticipation of a method of suppressing the immune system using an IL-27R agonist. Paragraph 39 reads as follows (emphasis added):

"IL-D80 or IL-27 agonists, or antagonists, may also act as functional or receptor **antagonists**. Thus, IL-D80, IL-27, WSX-1/TCCR, or its **antagonists**, may be useful in the treatment of abnormal medical conditions, including immune disorders, e.g., T cell immune deficiencies, inflammation, or tissue rejection, or in cardiovascular or neurophysiological conditions."

(Applicants note that "WSX-1" and "IL-27R" are both terms used to refer to the receptor for the cytokine IL-27.) The above paragraph from Timans refers only to the use of IL-27R antagonists in the treatment of immune conditions, not an agonist as claimed. Although the paragraph refers to agonists, it does not specifically teach their use to treat an immune disorder, much less to treat someone in need of immune suppression.

The Office also referred to paragraph 135 for a teaching regarding agonist antibodies to IL-27R.

"Drug screening using IL-D80, IL-27, WSX-1/TCCR or fragments thereof can be performed to identify compounds having binding affinity to or other relevant biological effects on IL-D80 or IL-27 functions, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the cytokine. Likewise, a compound having intrinsic stimulating activity can activate the signal pathway and is thus an agonist in that it simulates the activity of IL-D80 or IL-27. This invention further contemplates the therapeutic use of blocking antibodies to IL-D80, IL-27, or WSX-1/TCCR as antagonists and of stimulatory antibodies as agonists. This approach should be particularly useful with other IL-D80 or IL-27 species variants."

This paragraph does no more than define an agonist as a compound having stimulating activity and teach that biological assays can determine whether a compound is an agonist or antagonist. Applicants do not dispute that it is well known in the art that such antibodies can be produced, tested, and screened for therapeutic activity. However, a generic statement indicating that agonist antibodies to IL-27R can be made and identified and used in immune disorders does not teach the specific use of agonist antibodies to IL-27R as presently claimed. The final sentence in the paragraph mentions a therapeutic use for agonist antibodies, but does not state what that therapeutic use might be. The art at the time the application was filed and Timans as a whole clearly show that immune suppression was not a contemplated use for an agonist antibody to IL-27R. If any use was considered for agonists of IL-27R, it was as an activator of the immune system, the opposite of the claimed invention.

Paragraph 161 (emphasis added) of Timans is also referenced in the Action as support for the anticipation rejection.

"Taken together the above indicates a role for the composite cytokine and its associated receptor subunit WSX-1/TCCR in inflammatory responses. Therefore **antagonizing the function of any of the components in the receptor subunit:ligand complex should have a beneficial effect in inflammatory diseases, e.g., inflammatory bowel disease, rheumatoid arthritis, etc.**"

This paragraph further highlights that Timans, if anything, advocates a role for an **antagonist** of IL-27R in any treatment of an inflammatory response. The claimed methods are drawn to using an **agonist** of IL-27R to treat an inflammatory response and therefore are clearly not anticipated by Timans.

In conclusion, Timans does not teach using an agonist of IL-27R for immune suppression. When viewed in its entirety, Timans, like the other prior art available at the time of the claimed invention, teaches the use of an **antagonist** for immune suppression. Therefore, it cannot anticipate the claimed invention drawn to a method of using an IL-27R agonist for immune suppression; and Applicants respectfully request that the rejection be withdrawn.

The claims are not anticipated by De Sauvage

The claims were rejected as allegedly anticipated by De Sauvage. However, De Sauvage teaches a role for IL-27R in the differentiation of Th1 and Th2 cells, not a role in immune suppression, as presently claimed. Therefore, De Sauvage does not teach the administration of an IL-27R agonist to a patient in need of immune suppression as presently claimed. Because De Sauvage teaches that such a ligand would alter the balance of the immune response, not suppress the response as claimed, there is nothing in De Sauvage to teach or suggest that patients in need of immune suppression be treated with an IL-27R agonist as claimed.

While agonist antibodies of IL-27R may be discussed in De Sauvage, the agonists are advocated to promote differentiation of helper T cells, not to modulate an immune response as claimed, e.g., independent of the polarization of the immune response. De Sauvage claims that agonists and antagonists to IL-27R shift the balance between Th1 and Th2 type immune responses. This does not provide immune suppression as claimed, merely polarization of the immune response. An agonist or antagonist is not administered in De Sauvage to suppress the immune system; they administer the agonist/antagonist to switch the type of immune response a patient experiences. Therefore, De Sauvage does not teach every element of the claimed invention.

In alleging that De Sauvage anticipates the claimed invention, the Action relies on standard teachings related to making agonist antibodies to IL-27R (pages 51-56), and the definition of an immune related disease on page 8 for anticipation of the claimed invention. Applicants acknowledge that any definition of immune related diseases or disorders will most likely include a suggestion of immune suppression in some situations.

However, De Sauvage does not teach the specific use of an agonist for immune suppression. In fact, it specifies that an IL-27R agonist be used to polarize an immune response, e.g., shift it from a Th2 mediated response to a Th1 mediated response, but not to suppress the immune system as claimed. Although De Sauvage, e.g., on page 8 and page 9, lists treatment of various inflammatory diseases, it in no way specifies that suppression of an inflammatory immune response should constitute treatment with an agonist of IL-27R. This does not teach immune suppression with an agonist as claimed.

While De Sauvage may teach how to make an agonist antibody to IL-27R and state that such agonists could play a role in treatment of immune disorders, it does not teach or suggest that such an agonist should be given to a patient in need of immune suppression. If anything, it teaches that an agonist of IL-27R should be given to a patient in need of Th1 activation, not immune suppression as presently claimed. Therefore, De Sauvage does not anticipate the claimed invention and Applicants respectfully request that the rejection be withdrawn.

The claims are not anticipated by Bennet.

The claims were also rejected as allegedly anticipated by Bennet. Bennet, if anything, discloses an IL-27 cytokine receptor, but it does not teach its use in suppressing the immune system through activation of IL-27R. Therefore, Bennet does not teach every element of the claims and cannot anticipate the claimed invention.

Page 4 of Bennet is cited in the Action to support the anticipation rejection. However, page 4 merely provides the generic and well-known fact that an agonist antibody can be used to activate an IL-27 receptor. This does nothing more than state what anyone skilled in the art would know.

Bennet also states that the agonist antibody can be used to "treat conditions in which an effective amount of WSX receptor activation leads to a therapeutic benefit" and lists specific conditions in which agonists might be helpful. In fact, it specifies using an agonist when **stimulation or proliferation** of stem cells is desired or to treat metabolic disorders or conditions characterized by a decrease in blood cells. See, e.g., page 4, lines 14-

23 and page 56, lines 24-33. The use of IL-27R agonists is not suggested for immune suppression.

The Office also specifically cited page 6 as anticipating the claimed invention. However, page 6 of Bennet states that leukemia and lymphoma are treated with antagonist antibodies, not agonists as presently claimed. Pages 56-59 are also referenced to allege that the agonists are used for suppression of the immune system. Applicants respectfully disagree. The pages do indeed contain a long list of conditions that may be treated by either agonist or antagonist antibodies of IL-27R. However, upon close review, it is clear that for patients in need of immune suppression, the antagonist treatment is suggested, not the agonist as presently claimed. Bennet, along with other prior art available at the time of Applicants' invention, urges the use of an antagonist of IL-27R for immune suppression and if anything only vaguely alludes to a use for an agonist of IL-27R.

In addition, there appears to be some confusion in the Action regarding conditions to be treated in the claimed methods verses those discussed in the prior art. In all the claimed methods, the agonist is used to suppress an immune response. A patient may be suffering from any of a wide range of disorders and be in need of immune suppression. However, the claims are amended herein, as suggested by the Examiner, to clarify which disorders are those in which immune suppression is especially desired. Therefore, the claimed invention is not anticipated by Bennet and Applicants respectfully request that the rejection be withdrawn.

The claims are not anticipated by Matthews

The claims were also rejected as allegedly anticipated by Matthews. Matthews describes the use of the cytokine receptor, IL-27R, in enhancing the proliferation or differentiation of hematopoietic cells. A patient in need of immune suppression was not selected for treatment in Matthews because it was unknown in the prior art that an agonist of IL-27R could be used for immune suppression. Therefore, Matthews does not teach a method of treatment involving administration of an IL-27R agonist for suppression of the immune system as presently claimed and does not anticipate the claimed invention.

In Matthews, any patients selected for treatment with an agonist to IL-27R would be selected because of their need for **enhanced proliferation** of blood cells.

Although Matthew lists some of the same diseases as the present claims, the patients suffering from those diseases are selected because of their need for blood cell proliferation.

The passages in Matthews to which the Action refers do nothing more than indicate that an agonist antibody to IL-27R can be used to **stimulate proliferation** of cells, e.g., to activate IL-27R. For example, at column 44, line 22, (emphasis added), Matthew states:

The **WSX receptor** (polypeptide or nucleic acid) **can be used to induce proliferation and/or differentiation of cells in vitro**. In particular, it is contemplated that this molecule may be used to induce proliferation of stem cell/progenitor cell populations (e.g. CD34+ cell populations obtained as described in Example 8 below). These cells which are to be grown ex vivo may simultaneously be exposed to other known growth factors or cytokines, such as those described herein. **This results in proliferation and/or differentiation of the cells having the WSX receptor.**"

Applicants fail to see how the teaching that the WSX receptor induces proliferation of cells having the receptor teaches immune system suppression as claimed or selection of a patient in need of immune suppression. Furthermore, as provided in column 45, lines 55-58, also quoted in the Action.

"Such agonists or antagonists may constitute potential therapeutics for treating conditions characterized by insufficient or excessive WSX receptor activation, respectively."

This merely states the obvious, that agonists activate and antagonists deactivate a receptor. It does not explicitly state that activation of IL-27R can be used to suppress the immune system and there is nothing in the prior art to suggest that it would do so. Therefore, Matthews cannot anticipate the claimed invention and Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §102 should be withdrawn

Of all of the references, the most that can be said is that they teach the IL-27R receptor, its relation to IL-27 as a ligand, an unidentified role in disorders of the immune system, and perhaps a role in T cell differentiation, i.e., polarization of the T cell response. However, what is claimed is a new application for IL-27R in suppressing the immune system. To show anticipation, the Patent Office must show that the prior art teaches a connection between activation of IL-27R and suppression of the immune system (as provided

in the present application). This has not been shown by any of the references and therefore, none of the references anticipate the claimed invention.

Furthermore, the prior art references, when taken as a whole or individually, teach away from the claimed invention, because the state of the art at the time the application was filed was that IL-27R agonists could be used, if at all, to activate the immune system or polarize the T cell immune response. This teaches away from the claimed invention of using **agonists to suppress** the immune system.

To anticipate the claimed invention, the prior art must specify that the agonist be used to suppress the immune system. The prior art cited in the Action discusses both agonists and antagonists and list many immune disorders, including those that require immune suppression. The references cited discuss both immune suppression and immune activation, and agonists and antagonists. The art cited typically does not specify when an antagonist would be appropriate and when an agonist would be appropriate, and if anything recommends agonists for immune activation and antagonists for immune suppression. This is exactly opposite to the claimed invention and therefore, the art cited does not anticipate the claimed invention. Applicants therefore respectfully request that the rejections be withdrawn.

Appl. No. 10/768,744
Amdt. Dated December 10, 2007
Reply to Office action of August 9, 2007.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Respectfully submitted,


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Attachments:

- 1) A petition to extend the period of response for 1 months;
- 2) A transmittal sheet;
- 3) A fee transmittal sheet;
- 4) A receipt indication postcard.